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10/069,145	02/22/2002	Manja Ahola	TUR-125	7684

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EXAMINER

SHEIKH, HUMERA N

ART UNIT PAPER NUMBER

1615

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/069,145

Applicant(s)

AHOLA ET AL.

Examiner

Humera N. Sheikh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-13, 15 and 16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-13, 15 and 16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*. See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 C.F.R. 1.114, the Amendment, Applicant's Arguments/Remarks and the request for extension of time (1 month-granted), all filed 07/07/05 is acknowledged.

Claims 8-13, 15 and 16 are pending. Claims 8 and 12 have been amended. Claims 8-13, 15 and 16 are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/07/05 has been entered.

New Matter

The Amendment filed 07/07/05 raises the issue of new matter. The amendment to instant claim 8, line 7 presents new matter to the claims since it now recites '*up to 25 mol-%*'. There is lack of support for this amendment limitation in the specification. The specification at page 6, lines 13-15 recites 'In case *about 25%* of the amount of TEOS...' and the specification at page

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7, lines 20-21 recites "For the partial substitution of TEOS, *10 or 25 mol-%* was used". The claim recitation of 'up to 25 mol-%' is not supported by the ranges recited in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants claim a composition and method for the preparation of a composition comprising the partial replacement of a tetraalkoxysilane by an alkylsubstituted alkoxysilane. A review of the specification indicates that the only tetraalkoxysilane named and required to be replaced, is tetraethoxysilane (TEOS) (see pg. 6, lines 8-15). Therefore, the composition and process steps, which generically recite the partial replacement of a tetraalkoxysilane by an alkylsubstituted alkoxysilane are insufficient in written description and have not been presented in such a way so as to allow one of ordinary skill in the art to understand and practice the invention.

Claim Objections

Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 13, which is dependent upon independent claim 12 and corresponds to composition claim 9, fails to further limit the subject matter of claim 12 since it recites that the 'alkoxysilane is a tetraalkoxysilane'. It is suggested that claim 13 be amended to recite that the 'tetraalkoxysilane is a tetraethoxysilane (TEOS)', to be in similar scope as claim 9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.* (US Pat. No. 5,858,280) in view of Pinchuk *et al.* (US Pat. No. 5,804,318).

Zhang *et al.* teach a method for preparing methyl-modified silica gel using the sol-gel technology, and teach that the modified silica gel produced by the method of the invention have a three-dimensional network structure, which allows doping optically functional substances in high concentrations (see col. 2, lines 10-67).

According to Zhang *et al.*, a methyltrialkoxysilane, such as methyltriethoxysilane, may be combined with a tetraalkoxysilane, such as tetraethoxysilane, or a dialkoxysilane, such as dimethyldiethoxysilane, to control the size and polarity of spaces defined by the polysiloxane network (col. 3, lines 1-15).

Thus, with respect to the compositions claimed in claims 8-10 of the instant application, the prior art discloses modified silica gels obtained from a sol-gel and comprising a tetraalkoxysilane and an alkyl-substituted alkoxysilane, as claimed in claim 8, and a biologically active agent, wherein the tetraalkoxysilane is tetraethoxysilane, as claimed in claim 9, and the alkyl-substituted alkoxysilane is methyltriethoxysilane, as claimed in claim 10.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Zhang *et al.* is deficient in the sense that the patent does not provide heparin or a related acidic polysaccharide in the gel compositions of the invention and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the prior art teaches that the size of space defined by the polysiloxane network of the invention is particularly suitable to dope optical agents in high concentration (see col. 2, line 58 to col. 3, line 15), thus the patent provides the general teachings that gels formed from

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compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

With regard to the limitation in claim 8, that a carrier is a xerogel, Zhang *et al.* does not define the gels of the invention as xerogels, however, the patent contemplates drying the gel, as it teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (col. 2, lines 48-51). A xerogel is a dry polymerized gel, thus the patent contemplates producing silica xerogel carriers, as claimed by Applicant.

Zhang *et al.* is deficient in the sense that the patent does not provide heparin or a related polysaccharide in the gel compositions and methods of the invention. Additionally, with respect to claim 11, the patent fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant.

Pinchuk *et al.* ('318) provides a hydrogel coating bondable to an epoxy-functionalized surface of a medical device and comprising anti-thrombogenic agents (see col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (col. 2, lines 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin.

Thus, with regards to claims 8 and 11 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk *et al.* provides hydrogels comprising 2% heparin. The patent is deficient in the sense, that the reference fails to disclose an amount of 5-30%, calculated on the air-dried xerogel, as claimed by Applicant. Zhang *et al.* contemplates drying the gel, as the reference teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (see col. 2, lines 48-51). A xerogel is a dry polymerized gel. It is the view of the Examiner that during the process of air-drying, the gel loses water and concentration of the solutes in the gel increases as a result of the water loss. Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk *et al.* in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the gel compositions and method for producing said compositions disclosed by Zhang *et al.*, by including heparin in the gel compositions of the invention, as taught by Pinchuk *et al.*, to obtain a composition for the controlled release of heparin and a successful method for preparing said composition. Because of the teachings of Zhang *et al.*, that the gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxy silane are useful as carriers for biologically active agents and are resistant to drying, and the teachings of Pinchuk *et al.*, that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would

have a reasonable expectation that the compositions claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncova *et al.* (Collect. Czech. Chem. Commun.) in view of Pinchuk *et al.* (US Pat. No. 5,804,318).

The paper by Kuncova *et al.* discloses xerogels prepared using sol-gel procedures by hydrolysis of silicon alkoxides (see Abstract and p. 1573), and specifically includes tetraethoxysilane (TEOS), methyltriethoxysilane (METES) and dimethyldiethoxysilane (DMDES) among the alkoxides used in the research (See Solutions IV in Table 1, p. 1574). Thus, with respect to the carrier claimed in claims 8-10 of the instant application, the prior art provides xerogels derived from sol-gels and comprising tetraethoxysilane and alkyl-substituted alkoxysilanes, specifically methyltriethoxysilane and dimethyldiethoxysilane, as claimed by Applicant.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Kuncova *et al.* are deficient in the sense, that the paper does not provide heparin or a related acidic polysachharide in the xerogel compositions and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the prior art teaches that lipase, a biologically active agent, is immobilized in xerogel compositions and retain its activity for an extended period of time (see pp. 1574-1576 and Table 2). In

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particular, the reference teaches that the xerogel formed from solution IV, comprising TEOS and DMDES, is characterized by a higher activity of lipase as compared to other xerogels obtained from compositions not comprising the tetraethoxysilane or the alkyl-substituted alkoxysilane (see p. 1574, Table 1 and Table 2). Thus, the prior art provides the general teachings that xerogels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

Pinchuk *et al.* ('318) provides a hydrogel coating bondable to an epoxy-functionalized surface of a medical device and comprising anti-thrombogenic agents (see col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (col. 2, lines 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin. Thus, with regards to claims 8 and 11 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk *et al.* provides hydrogels comprising 2% heparin (see Example 3). The patent is deficient in the sense, that the reference fails to disclose an amount of

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5-30%, calculated on the air-dried xerogel, as claimed by Applicant. Zhang et al. contemplates drying the gel, as the reference teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (see col. 2, lines 48-51). A xerogel is a dry polymerized gel. It is the view of the Examiner that during the process of air-drying, the gel loses water and concentration of the solutes in the gel increases as a result of the water loss. Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk et al. in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the gel compositions disclosed by Kuncova et al., by including heparin in the gel compositions of the invention, as taught by Pinchuk et al., to obtain a composition for the controlled release of heparin. The expected result would have been a successful gel composition for the controlled release of heparin. Because of the teachings of Kuncova et al., that xerogel compositions prepared using sol-gel procedures by hydrolysis of silicon alkoxides, specifically TEOS, METES and DMDES, are useful carriers as biologically active agent, and the teachings of Pinchuk et al., that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would have a reasonable expectation that the compositions claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 07/07/05 have been fully considered but they are not persuasive.

Firstly, Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 8-11 over Zhang et al. (US '280) in view of Pinchuk et al. (US '318) stating, "The cited combination of references fails to raise a *prima facie* case of obviousness against the claimed composition because the cited references fail to disclose, teach or suggest the maximum 25 mol-% alkylsubstituted silane feature of the silica xerogel. One of ordinary skill in the art is given no motivation or disclosure to reduce the amount of alkylsubstituted alkoxy silane from 75 mole-% or 70 mole-% down to 25 mole-% or less. Pinchuk et al. also fails to disclose or suggest that an antithrombogenic agent such as heparin can be encapsulated into sol-gel derived xerogel derived from tetraalkoxysilane which has been co-hydrolyzed with up to 25 mol-% of an alkylsubstituted alkoxy silane, or that heparin may be controllably released from the xerogel. Pinchuk et al. discloses a surface coating comprising a non-silica hydrogel containing pendant primary and tertiary amine groups. The coating itself of Pinchuk et al. is not made of sol-gel derived silica xerogel derived from tetraalkoxysilane. There is no teaching or suggestion that heparin may be controllably released from a sol-gel derived silica xerogel derived from tetraalkoxysilane."

Applicant's arguments have been fully considered, but were not found persuasive. Applicant's argument that the 'cited combination of references fails to raise a *prima facie* case of obviousness against the claimed composition because the cited references fail to disclose, teach or suggest the maximum 25 mol-% alkylsubstituted silane feature of the silica xerogel' is not

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persuasive since the teachings of the prior art are not limited to the examples disclosed by the prior art. The teachings of the prior art, as a whole, are to be considered in determining patentability. Burden is upon Applicant to demonstrate that the instant 25 mol-% or less claimed, would provide for unexpected or superior results over the formulations of the prior art. Applicant's argument that 'Pinchuk et al. discloses a surface coating comprising a non-silica hydrogel and the coating itself is not made of sol-gel derived silica xerogel derived from tetraalkoxysilane' is not persuasive since Pinchuk et al. was relied upon for the teaching that it is well known in the art to incorporate a biologically active agent, such as heparin sulfate as the particular anti-thrombogenic agent in hydrogel compositions. Pinchuk et al. teach that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (col. 5, lines 13-21). The prior art also suggests that the size of space defined by the polysiloxane network of the invention is particularly suitable to dope optical agents in high concentration (see col. 2, line 58 to col. 3, line 15). Thus based on this teaching, the patent provides the general concept that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxyisilane are suitable carriers for biologically active agents.

Secondly, Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 8-11 over Kuncova et al. (Collect. Czech. Chem. Commun.) in view of Pinchuk et al. (US '318) stating, "A feature of the claimed biodegradable composition is the partial replacement of a tetraalkoxysilane with an alkylsubstituted alkoxyisilane. Kuncova et al. fails to disclose the partial replacement of a tetraalkoxysilane with up to 25 mol-% of an alkylsubstituted alkoxyisilane. Pinchuk et al. merely discloses a non-silica hydrogel bound to a surface to be coated by a silane coupling agent."

Applicant's arguments have been considered, but were not found persuasive. Applicant's argument that the 'Kuncova et al. fails to disclose the partial replacement of a tetraalkoxysilane with up to 25 mol-% of an alkylsubstituted alkoxysilane' is not persuasive since Applicants have not demonstrated that the instant 25 mol-% or less claimed, would provide for unexpected or superior results over the formulations of the prior art. Kuncova et al. teach xerogels prepared using sol-gel procedures by hydrolysis of silicon alkoxides (see Abstract and p. 1573), and specifically includes tetraethoxysilane (TEOS), methyltriethoxysilane (METES) and dimethyldiethoxysilane (DMDES) among the alkoxides used in the research (see Solutions IV in Table 1, p. 1574). The prior art provides xerogels derived from sol-gels and comprising tetraethoxysilane and alkyl-substituted alkoxysilanes, specifically methyltriethoxysilane and dimethyldiethoxysilane, as claimed by Applicant. Pinchuk et al. are relied upon for their teaching that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin. Thus, given the explicit teachings of the prior art, the instant invention is rendered *prima facie* obvious to one of ordinary skill in the art.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

H. N. Sheikh 

Patent Examiner

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September 12, 2005